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(71) Applicant *(for all designated States except US)*: **AUROBINDO PHARMA LIMITED** [IN/IN]; Plot No.2, Maitrivihar,, Ameerpet, Hyderabad 500038 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SINHA, Brajesh, Kumar** [IN/IN]; Aurobindo Pharma Limited, Plot No.2, Maitrivihar,, Ameerpet, Hyderabad 500038 (IN). **VADDI, Pandu, Ranga, Rao** [IN/IN]; Aurobindo Pharma Limited, Plot No.2, Maitrivihar,, Ameerpet, Hyderabad 500038 (IN). **BUDIDET, Sankar, Reddy** [IN/IN]; Aurobindo Pharma Limited, Plot No.2, Maitrivihar, Ameerpet, Hyderabad 500038 (IN). **DANDALA, Ramesh** [IN/IN]; Aurobindo Pharma Limited, Plot No.2, Maitrivihar,, Ameerpet, Hyderabad 500038 (IN). **MEENAKSHISUNDERAM, Sivakumaran** [IN/IN]; Aurobindo Pharma Limited, Plot No.2, Maitrivihar,, Ameerpet, Hyderabad 500038 (IN).

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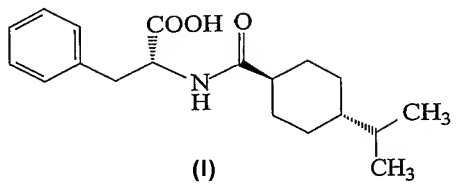
(54) **Title:** PROCESS FOR PREPARING NATEGLINIDE B-TYPE CRYSTALS



(I)

(57) **Abstract:** An improved process for preparing (-)-N-[(trans-4-isopropylcyclohexane)carbonyl]-D-phenylalanine of Formula I.

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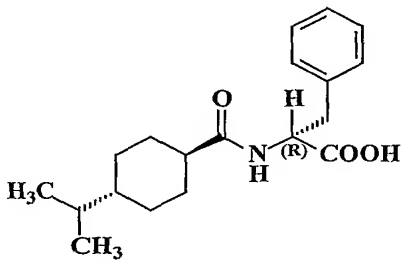
PROCESS FOR PREPARING NATEGLINIDE B-TYPE CRYSTALS

FIELD OF THE INVENTION

The present invention relates to an improved process for preparing essentially B-type crystals of (-)-N-[(trans-4-isopropylcyclohexane)carbonyl]-D-phenylalanine of Formula I.



Formula I

BACKGROUND OF THE INVENTION

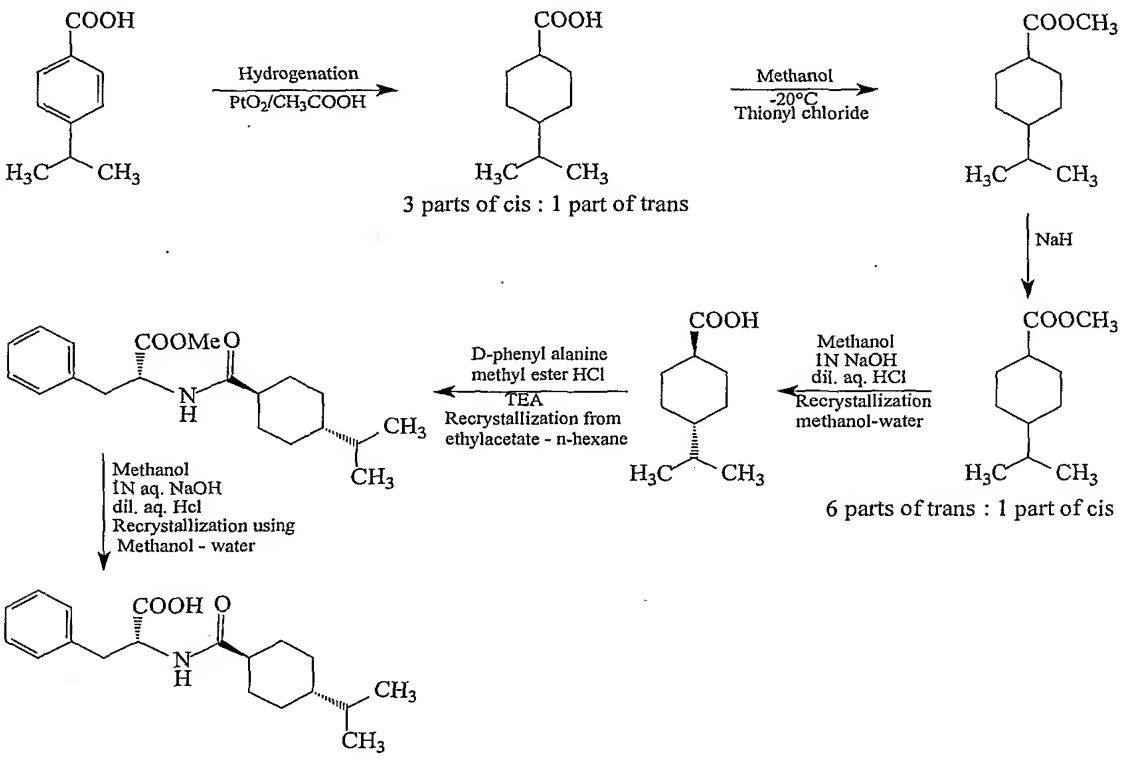
(-)-N-[(trans-4-Isopropylcyclohexane)carbonyl]-D-phenylalanine of Formula I, which is generically known as Nateglinide is an antidiabetic drug. Nateglinide is being marketed under the name STARLIX as an oral tablet.

Nateglinide was first disclosed in RE 34,878 and the crystals thus produced in this patent are named as B-type crystals, in a subsequent patent US 5,463,116.

In view of the importance of Nateglinide as an antidiabetic compound, several synthetic methods have been reported in the literature to prepare B-type crystals, which are as summarized below:

RE 34,878 discloses a method of preparing Nateglinide in example 31. The process comprises hydrogenating cumic acid to produce a cis/trans mixture of 4-isopropylcyclohexane carboxylic acid, wherein the cis isomer is in 3 parts and trans

isomer in 1 part. This mixture is esterified and treated with sodium hydride to increase the trans isomer ratio to 6 parts to 1 part of cis isomer. This product is hydrolysed and coupled with D-phenylalanine methyl ester. The resulting product is desterified to give Nateglinide. The process is as shown below:



The above process is a multistep process, with low yields and poor quality of the Nateglinide. Further, technology involved in some of the steps of above process are tedious to work-up.

US 5,463,116 discloses a process to prepare Nateglinide B-type crystals in comparative example A2, which comprises dissolving Nateglinide in a mixture of ethanol and water at 30°C and further cooling the reaction mass to 5°C. The resulting

precipitated crystals were filtered and dried at 90°C under reduced pressure overnight to yield Nateglinide B-type crystals.

EP 1 535 900 A1 discloses a process to prepare Nateglinide, by reacting D-phenylalanine methyl ester or a salt thereof with trans-4-isopropyl cyclohexane carboxylic acid in presence of an acyl chloride in a water-miscible organic solvent or water non-miscible organic solvent to give Nateglinide methylester. Nateglinide methylester thus obtained was hydrolysed to Nateglinide and further converted to sodium salt of Nateglinide. The sodium salt was further converted to Nateglinide hydrochloride salt by treating with an hydrochloric acid at room temperature, preferably in the temperature range from 5 °C to 20 °C, such that Nateglinide in the pure B-type precipitates therefrom. This process uses a toxic reagent thionyl chloride, which is corrosive, moisture sensitive and not eco-friendly.

WO 2004/018408 A1 discloses a process to prepare Nateglinide, by reacting trans-4-isopropyl cyclohexyl carboxylic acid in acetone with alkyl chloroformate in the presence of triethylamine to give a solution of trans-4-isopropyl cyclohexyl carboxylic acid alkylformate and was reacted with alkali solution of D-phenylalanine to give Nateglinide and is further purified and then converted to H-type crystals. The yields of pure Nateglinide B-type crystals are in the range of 50-60 %. This B-type crystals are further converted in to H-type crystals with an average yield of 45 %.

US 2003/0229249 A1 claims a process to prepare Nateglinide B-type crystals, which comprises drying solvated materials containing Nateglinide hydrates obtained by crystallizing out from a Nateglinide containing solution under cooling at a temperature of 50°C or lower until no solvent remains and heating the resultant at a temperature of 60 to 110°C to yield Nateglinide B-type crystals.

WO 2005/113485 A1 claims a process to prepare Nateglinide B-type crystals, which comprises dissolving Nateglinide in an alcohol or ketone solvent and adding the Nateglinide solution to hydrocarbon liquid at temperatures 40 to 45°C and thereafter adding water and cooling the reaction mass to yield Nateglinide B-type crystals.

We have now found an improved process to prepare Nateglinide and also in single crystalline B-type crystals, which is industrially feasible, with good yields and good quality. In addition to the above processes, the present invention is easy to handle and economically viable.

OBJECTIVE

The objective of the present invention is to provide an improved process for preparing Nateglinide.

In yet another objective of the present invention is to provide an improved process for preparing Nateglinide in B-type crystals.

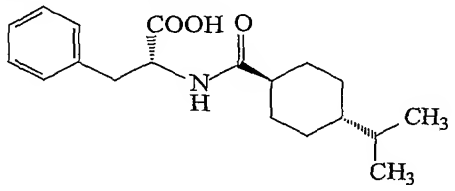
In yet another objective of the present invention is to provide an improved process for preparing Nateglinide B-type crystals, which is simple, industrially applicable and economically viable.

In yet another objective of the present invention is to provide a process for the manufacture of pure Nateglinide B-type crystals free from other crystals.

In yet another objective of the present invention is to provide an improved process for preparing Nateglinide, which is free of 2-[2-[(trans-4-isopropylcyclohexanecarbonyl)amino]-3-phenylpropionylamino]-3-phenylpropionic acid (IPP).

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a process for preparing essentially B-type crystals of Nateglinide of Formula I,



Formula I

which comprises,

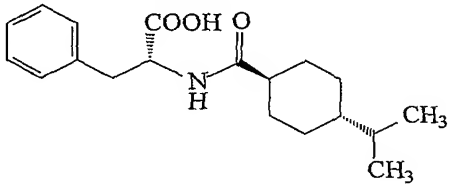
a) stirring the wet Nateglinide in an hydrocarbon solvent;

b) drying the solvated Nateglinide at a temperature below 40°C till the moisture content is above 7 % w/w;

c) further drying at 55 to 65°C till moisture content is less than 5%; and

d) thereafter drying at 60 to 90°C to yield Nateglinide B-type crystals free from other crystals

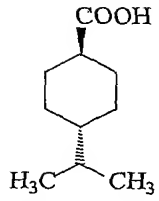
An embodiment of the present invention, relates to an improved process for preparing Nateglinide of Formula I,



Formula I

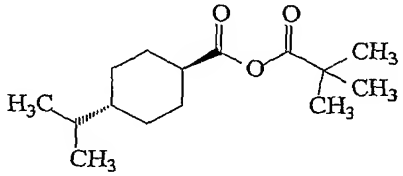
which comprises,

a) treating trans-4-isopropylcyclohexane carboxylic acid of Formula II,



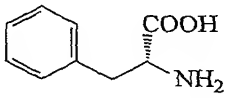
Formula II

with an alkali base and pivaloyl chloride in a solvent to give trans-4-isopropylcyclohexyl pivalic anhydride of Formula III;



Formula III

b) reacting trans-4-isopropylcyclohexyl pivalic anhydride of Formula III with D-phenylalanine solution of Formula IV;



Formula IV

in the presence of alkali base to give Nateglinide of Formula I.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention as described within the frame of the present application may be better understood with reference to the enclosed Figures, in which

Figure 1 is a DSC thermogram of wet Nateglinide

Figure 2 is a DSC thermogram of wet Nateglinide in cold heptane slurry

Figure 3 is a DSC thermogram of wet Nateglinide after drying at less than 40°C wherein the moisture content is above 7 % w/w.

Figure 4 is a DSC thermogram of wet Nateglinide after drying at 55-65°C wherein the moisture content is less than 5 % w/w

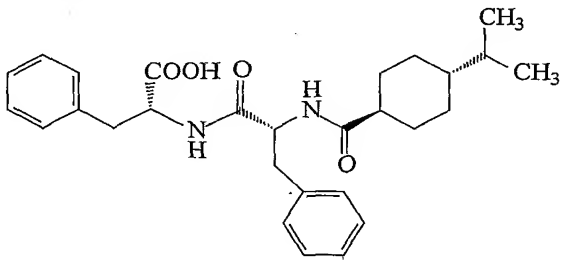
Figure 5 is a DSC thermogram of Nateglinide after drying at 80-90°C, which corresponds to B-type crystals.

DETAILED DESCRIPTION OF THE INVENTION

In an aspect of the invention the trans-4-isopropylcyclohexane carboxylic acid of Formula II is treated with a alkali base and a solvent, which is selected from toluene, acetone and mixtures thereof. The obtained product is treated with pivaloyl chloride to obtain trans-4-isopropylcyclohexyl pivalic anhydride of Formula III. The alkali base is selected from sodium hydroxide or potassium hydroxide. The base can be added as such or as an aqueous solution. The reaction is carried out at 0-30°C, preferably at 20-30°C. The trans-4-isopropylcyclohexyl pivalic anhydride of Formula III may be isolated from the reaction mass or can be directly treated with D-phenylalanine solution of Formula IV in the presence of alkali base at pH 10.0-14.0 and at 10-40°C to produce Nateglinide of Formula I. Preferably the pH is at 11-13 and temperature at 20-30°C.

The Nateglinide isolated by the above process is free from H-type crystals and is further purified and dried to yield a single form preferably B-type crystals.

Further, the Nateglinide produced as per the process of the present invention is free of 2-[2-[(Trans-4-isopropylcyclohexanecarbonyl)amino]-3-phenylpropionylamino]-3-phenylpropionic acid (IPP) of Formula V,



Formula V

This is achieved by maintaining the reaction mass pH at 10.0-14.0 during condensation of trans-4-isopropylcyclohexyl pivalic anhydride of Formula III and D-phenylalanine solution of Formula IV.

In another aspect of the present invention, the D-phenylalanine solution is prepared by treating D-phenylalanine with sodium hydroxide in the presence of a solvent and water. The solvent used to prepare sodium salt of D-phenylalanine is acetone.

In another aspect of the present invention Nateglinide is suspended in a mixture of water and aqueous alkali hydroxide at 30-35°C. To this solution cold dilute hydrochloric acid is added at 5-10 °C. The precipitated product is filtered and washed with cold water till it is free of chlorides. This wet product is slurried in cold hydrocarbon solvent and stirred at 0-10°C for 2 h. The solid product is filtered, washed with cold hydrocarbon solvent and dried at different temperatures so as to yield exclusively B-type crystals. The hydrocarbon solvent is selected from substituted or unsubstituted cyclic or acyclic C_5 to C_{10} alkyl, such as hexane, heptane, cycloheptane, cyclohexane and mixtures thereof. The most preferred hydrocarbon solvent employed is heptane.

In the drying process, the wet product is initially dried at below 40°C till the moisture content is above 7 %. Subsequently, the drying temperature is raised to 55-65°C until the moisture content of Nateglinide is below 5%. Then the product is finally dried at temperature range of 60-90°C, and more preferably at 80-90°C to result in pure Nateglinide B-type crystals substantially free from other crystals. The grade of polymorphic purity of the product obtained by the present process has been evaluated by DSC analysis showing only one peak specific for the B-type crystal of Nateglinide.

The present invention allows for providing a process for the preparation of Nateglinide in B-type substantially free from other types of crystals starting from solvated wet Nateglinide that initially shows only one broad endothermic peak (Figure 1). The wet solvated Nateglinide upon stirring in cold heptane, an endotherm

peak attributing to B-type crystals slowly appears along with an intermediate peak at 103-104 °C (Figure 2). After the cold heptane slurry this solvated wet Nateglinide is dried at below 40°C till the moisture content is above 7 % w/w (Figure 3) and subsequently at 55-65°C until the moisture content is less than 5 % w/w (Figure 4). Finally this material is further dried at 60-90°C wherein all the intermediate endotherm peaks are transformed to give only one single endotherm peak, which is attributed to the B-type crystals (Figure 5).

The major advantage of the process of the present invention is obtaining exclusively B-type crystals in good yields requiring no further chemical purification. Also in the process of the present invention the inventors have observed that wet Nateglinide when stirred with a hydrocarbon solvent B-type crystal seeds were generated thus facilitating the conversion of the remaining polymorphic mixture to exclusively B-type upon drying at various temperature ranges.

The invention is illustrated with the following examples, which are provided by way of illustration only and should not be construed to limit the scope of the invention.

EXAMPLE 1

PREPARATION OF NATEGLINIDE

Trans-4-isopropylcyclohexane carboxylic acid (50 g) was dissolved in acetone (300 ml) and treated with 40% w/w aqueous sodium hydroxide solution (30.81 g) at 20-30°C. The reaction mass was stirred for 30 min and cooled to 10-15°C. Pivaloyl chloride (39 g) was added to the reaction mass at 10-15°C and allowed to 20-25°C and stirred for 3 h, filtered and washed with acetone (25 ml). The filtrate containing trans-4-isopropylcyclohexyl carboxylic pivalic anhydride was added to the mixture of D-phenylalanine (53.4 g), DM water (300 ml), acetone (100 ml) and 10% w/w aqueous sodium hydroxide solution (130 g) at 20-25°C in 30 min while maintaining

the reaction mass pH at 11.5-12.5 with 10% w/w aqueous sodium hydroxide solution (130 g). The reaction mass was stirred for completion of reaction and distilled out acetone under reduced pressure. The residue was diluted with DM water (750 ml) and acidified with 10% w/v aqueous hydrochloric acid till the pH 1.0-2.0. The precipitated product was filtered and washed with DM water (150 ml). The wet product was treated with DM water (2000 ml) followed by n-heptane (1000 ml) and dried to yield Nateglinide as B-type crystals.

Yield: 72 g (77.23 %)

EXAMPLE 2

PREPARATION OF NATEGLINIDE

Trans-4-isopropylcyclohexane carboxylic acid (120 g) was dissolved in toluene (600 ml) and treated with 40% w/w aqueous sodium hydroxide solution (74.2 g) at 20-30°C. The reaction mass was heated to reflux temperature and water was separated azeotropically. Toluene was distilled out completely from the reaction mass under reduced pressure and cooled to 40-50°C. The reaction mass was treated with acetone (480 ml) followed by pivaloyl chloride (90.94 g) at 10-15°C. The reaction mass stirred for 5 h for completion of reaction at 25-30°C, filtered and washed with acetone (25 ml). The filtrate containing trans-4-isopropylcyclohexyl carboxylic pivalic anhydride was added to the mixture of D-phenylalanine (128.0 g), DM water (720 ml), acetone (240 ml) and 10% w/w aqueous sodium hydroxide solution (335 g) at 20-30°C in 30 min while maintaining the reaction mass pH at 11.5-12.5 with 10% w/w aqueous sodium hydroxide solution (335 g). The reaction mass was stirred for completion of reaction and distilled out acetone under reduced pressure. The residue was diluted with DM water (1800 ml) and acidified with 10% w/v aqueous hydrochloric acid till the pH 1.0-2.0. The precipitated product was filtered and washed with DM water (150 ml). The wet product was treated with DM water

(10800 ml) followed by n-heptane (4320 ml) and dried to yield Nateglinide as B-type crystals.

Yield: 160 g (71.5 %)

Chromatographic purity: 99.94 %

EXAMPLE 3

PREPARATION OF NATEGLINIDE B-TYPE CRYSTALS

Nateglinide (10 g, 0.0315 mole) was dissolved in a mixture of DM water (100 ml) and 10% w/w aqueous sodium hydroxide (13.5 g) at 30-35°C. The solution was added to the cold dilute hydrochloric acid (2.5% w/v, 55 ml) at 5-10°C. The precipitated product was filtered, washed with cold DM water till it is free of chlorides. The wet product was added to the cold n-heptane (80 ml) and stirred at 0-10°C for 2 h. The solid product was filtered and washed with cold n-heptane (20 ml). The wet product was dried at 20-40°C till 7.2% w/w of moisture content was achieved and then dried at 55-65°C till <1% w/w of moisture content was achieved. The product was further dried at 80-90°C to obtain pure Nateglinide B-type crystals.

Yield: 9.5 g

EXAMPLE 4

PREPARATION OF NATEGLINIDE B-TYPE CRYSTALS

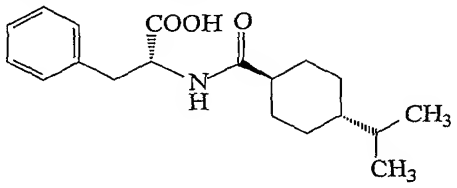
Nateglinide (10 g, 0.0315 mole) was dissolved in a mixture of DM water (100 ml) and 10% w/w aqueous sodium hydroxide (13.5 g) at 30-35°C. The solution was added to the cold dilute hydrochloric acid (2.5% w/v, 55 ml) at 5-10°C. The precipitated product was filtered, washed with cold DM water till it is free of chlorides. The wet product was added to the cold n-heptane (80 ml) and stirred at 0-10°C for 2 h. The solid product was filtered and washed with cold n-heptane (20 ml). The wet product was dried at 20-40°C till 7.2% w/w of moisture content was achieved and then dried at 55-65°C till <1% w/w of moisture content was achieved.

The dry product was mixed with cold n-heptane (70 ml), stirred for 1 h at 0-5°C, filtered, washed with cold n-heptane (20 ml) and dried at 20-40°C till constant weight was obtained. The product was further dried at 80-90°C to obtain pure Nateglinide B-type crystals.

Yield: 9.0 g

WE CLAIM:

1) The process for preparing essentially B-type crystals of Nateglinide of formula I,



Formula I

which comprises

a) stirring the wet Nateglinide in a hydrocarbon solvent;

b) drying the solvated Nateglinide at a temperature below 40°C till the moisture content is above 7 % w/w;

c) further drying at 55 to 65°C till moisture content is less than 5%; and

d) thereafter drying at 60 to 90°C to yield Nateglinide B-type crystals free from other crystals.

2) The process according to claim 1, wherein the hydrocarbon solvent is selected from substituted or unsubstituted cyclic or acyclic C_5 to C_{10} alkyl groups.

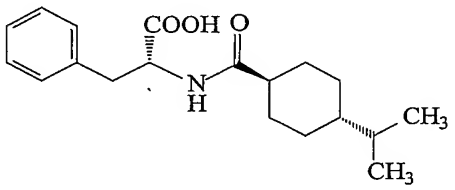
3) The process according to claim 2, the hydrocarbon is selected from hexane, heptane, cyclopentane, cyclohexane and mixtures thereof, more preferably heptane.

4) The process according to claim 1, wherein the drying temperature in step (b) is in the range of 20-40°C.

5) The process according to claim 1, wherein the drying temperature in step (d) is in the range of 80-90 °C.

6) The process according to claim 1, wherein the resulting B-type crystals of Nateglinide are devoid of other crystals as detected by DSC.

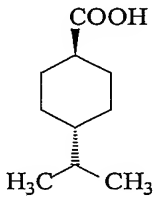
7) A process for preparing Nateglinide of Formula I,



Formula I

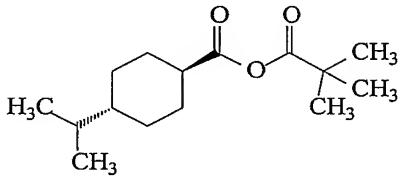
which comprises,

a) treating trans-4-isopropylcyclohexane carboxylic acid of Formula II,



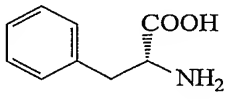
Formula II

with an alkali base and pivaloyl chloride in a solvent to give trans-4-isopropylcyclohexyl pivalic anhydride of Formula III;



Formula III

b) reacting trans-4-isopropylcyclohexyl pivalic anhydride of Formula III with D-phenylalanine solution of Formula IV;



Formula IV

in the presence of an alkali base to give Nateglinide of Formula I.

8) The process according to claim 7, wherein the alkali base is selected from sodium hydroxide, potassium hydroxide, preferably sodium hydroxide.

9) The process according to claim 7, wherein the solvent used in step (a) is selected from toluene, acetone and mixtures thereof.

10) The process according to claim 7, wherein the reaction of step (a) is carried out at temperature 0-30°C, preferably at 20-30°C.

11) The process according to claim 7, wherein the reaction of step (b) is carried out at temperature 10-40°C, preferably at 20-30°C.

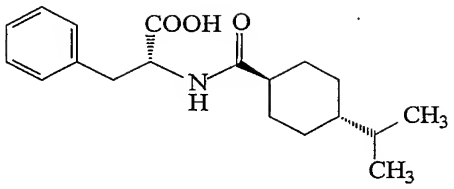
12) The process according to claim 7, wherein the D-phenylalanine solution is prepared by treating D-phenylalanine with sodium hydroxide in the presence of a solvent and water.

13) The process according to claim 12, the solvent used is acetone.

14) The process according to claim 7, wherein the pH of the reaction mass is maintained at 10.0-14.0, preferably 11.0-13.0 during condensation of trans-4-isopropylcyclohexyl pivalic anhydride and D-phenylalanine solution.

15) The process according to claim 1, wherein wet Nateglinide is prepared using a process claimed in Claim 7.

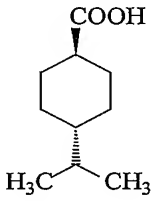
16) A process for preparing B-type crystals of Nateglinide of Formula I,



Formula I

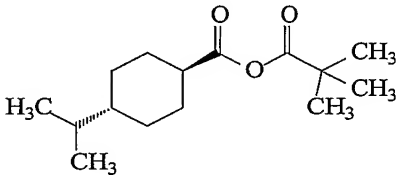
which comprises,

a) treating trans-4-isopropylcyclohexane carboxylic acid of Formula II,



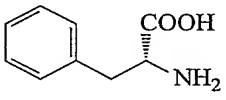
Formula II

with an alkali base and pivaloyl chloride in a solvent to give trans-4-isopropylcyclohexyl pivalic anhydride of Formula III;



Formula III

b) reacting trans-4-isopropylcyclohexyl pivalic anhydride of Formula III with D-phenylalanine solution of Formula IV;



Formula IV

in the presence of an alkali base to give wet Nateglinide;

c) stirring the wet Nateglinide in a hydrocarbon solvent;

d) drying the solvated Nateglinide at a temperature below 40°C till the moisture content is above 7 % w/w;

e) further drying at 55 to 65°C till moisture content is less than 5%; and

f) thereafter drying at 60 to 90°C to yield Nateglinide B-type crystals free from other crystals.

17) The process according to claim 16, wherein the alkali base is selected from sodium hydroxide, potassium hydroxide, preferably sodium hydroxide.

18) The process according to claim 16, wherein the solvent used in step (a) is selected from toluene, acetone and mixtures thereof.

19) The process according to claim 16, wherein the reaction of step (a) is carried out at temperature 0-30°C, preferably at 20-30°C.

20) The process according to claim 16, wherein the reaction of step (b) is carried out at temperature 10-40°C, preferably at 20-30°C.

21) The process according to claim 16, wherein the D-phenylalanine solution is prepared by treating D-phenylalanine with sodium hydroxide in the presence of a solvent and water.

22) The process according to claim 21, the solvent used is acetone.

23) The process according to claim 16, wherein the pH of the reaction mass is maintained at 10.0-14.0, preferably 11.0-13.0 during condensation of trans-4-isopropylcyclohexyl pivalic anhydride and D-phenylalanine solution.

24) The process according to claim 16, wherein the hydrocarbon solvent is selected from substituted or unsubstituted cyclic or acyclic C_5 to C_{10} alkyl groups.

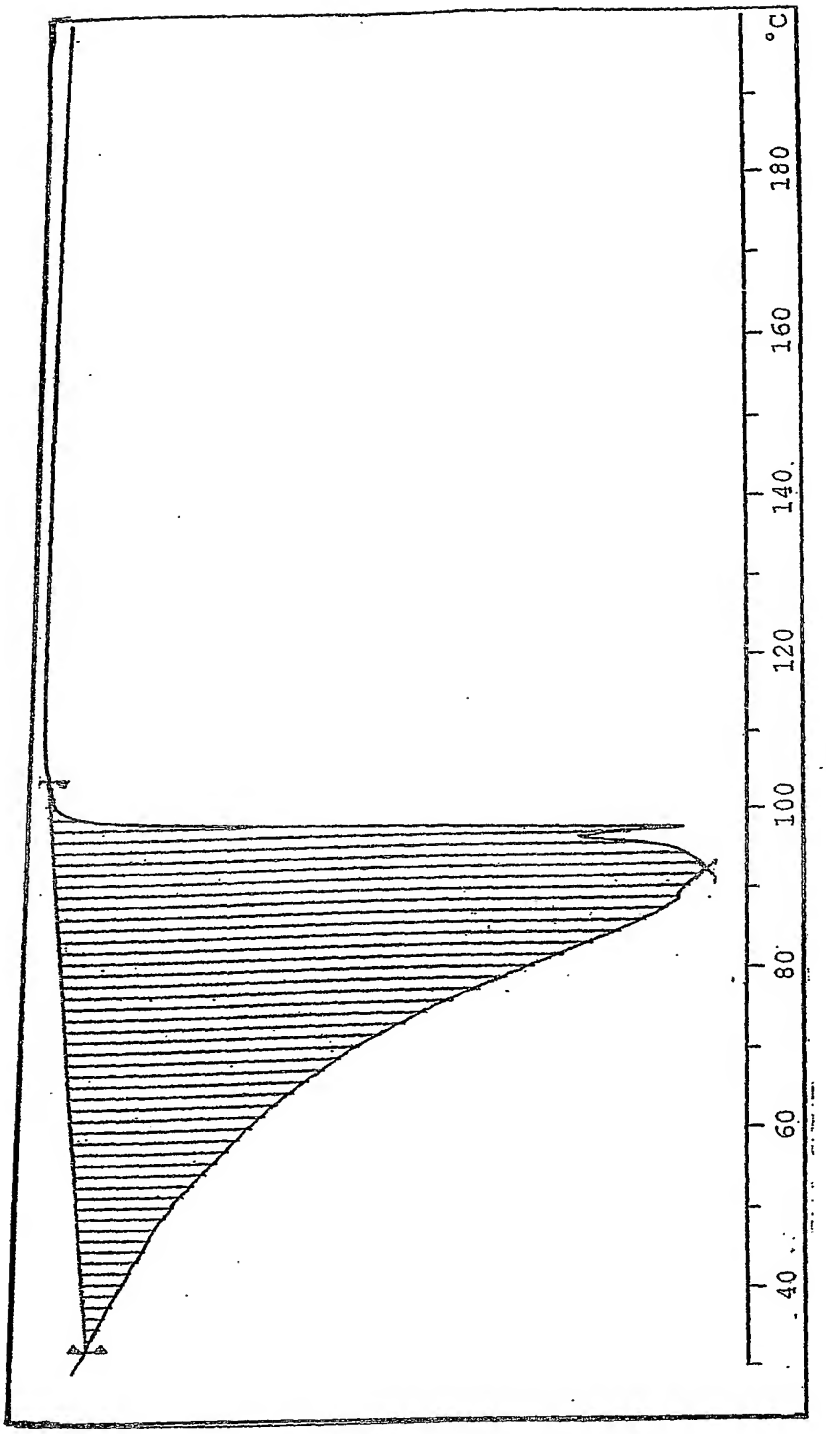
25) The process according to claim 24, the hydrocarbon is selected from hexane, heptane, cyclopentane, cyclohexane and mixtures thereof, more preferably heptane.

26) The process according to claim 16, wherein the drying temperature in step (d) is in the range of 20-40°C.

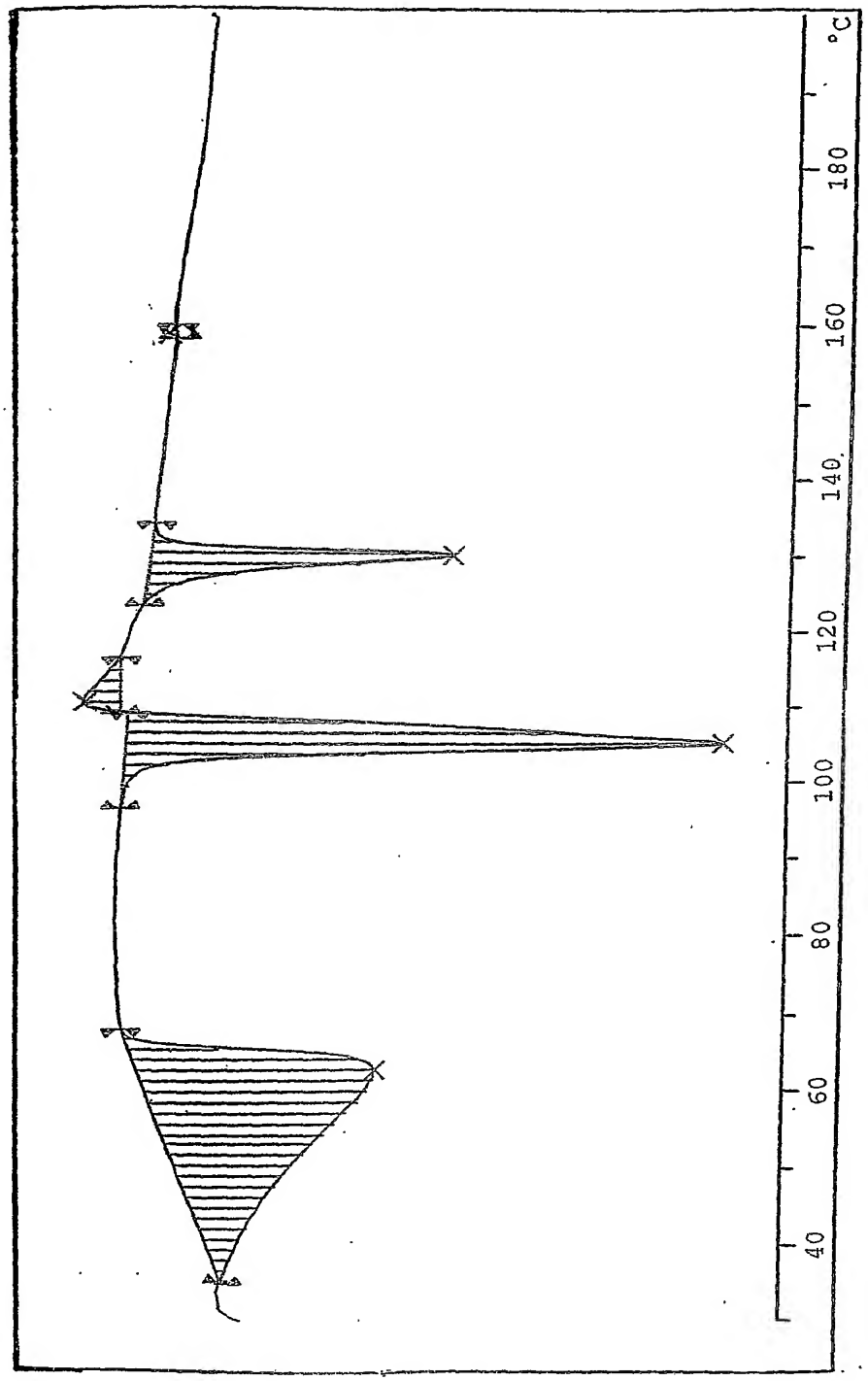
27) The process according to claim 16, wherein the drying temperature in step (f) is in the range of 80-90 °C.

28) The process according to claim 16, wherein the resulting B-type crystals of Nateglinide are devoid of other crystals as detected by DSC.

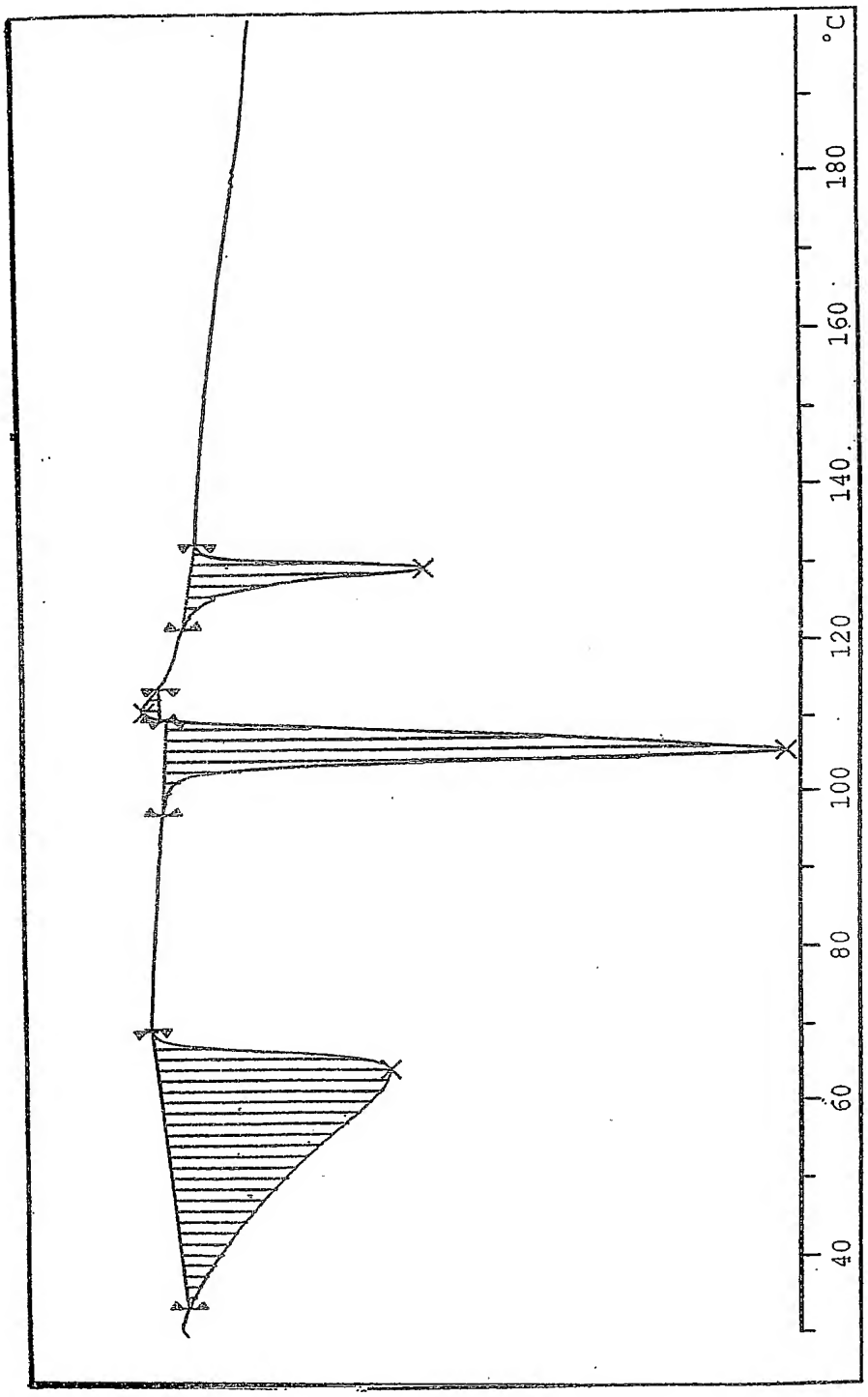
SHEET 1 OF 5



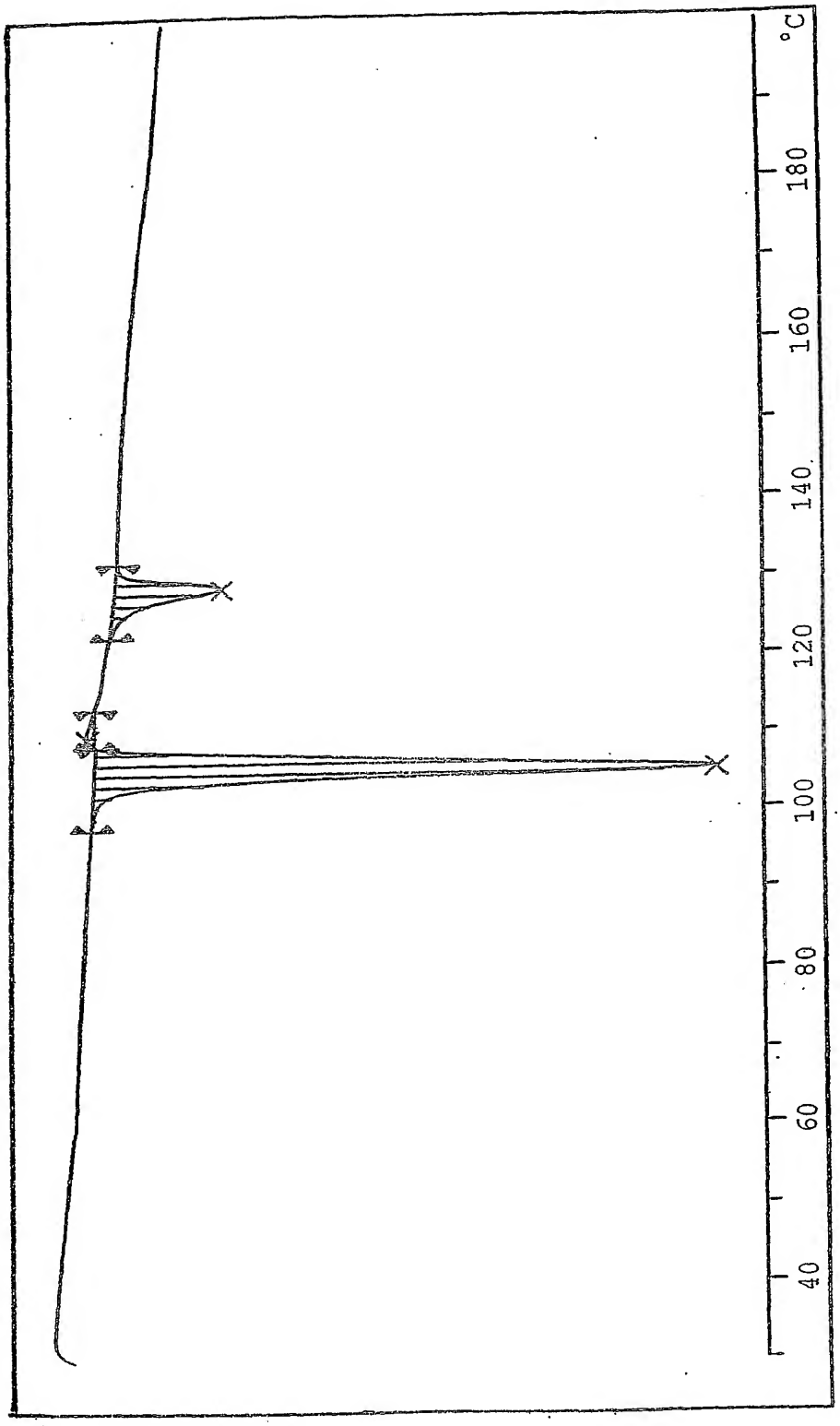
SHEET 2 OF 5



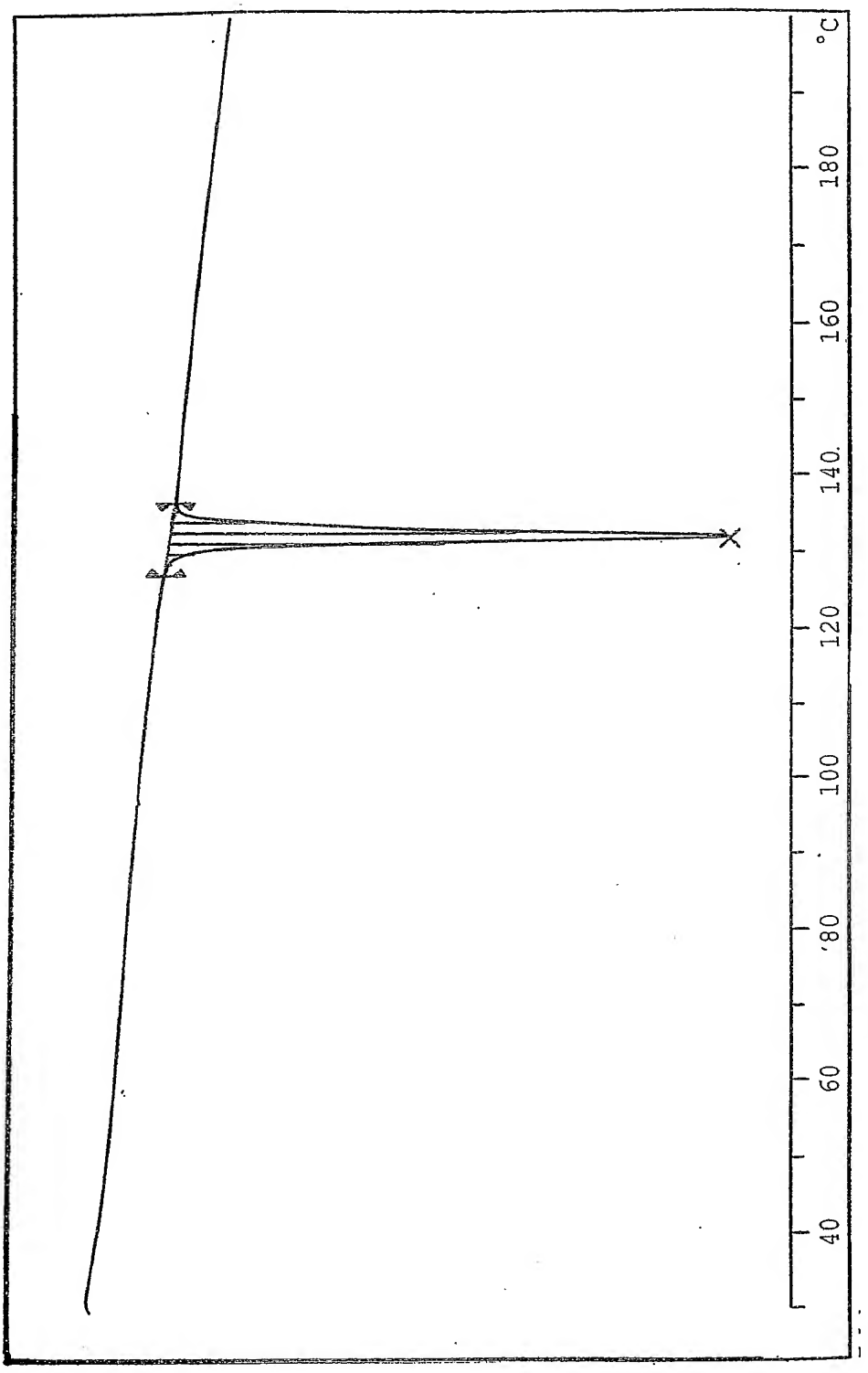
SHEET 3 OF 5



SHEET 4 OF 5



SHEET 5 OF 5



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/001301

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C231/02 C07C233/63

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/229249 A1 (SUMIKAWA MICHITO [JP] ET AL) 11 December 2003 (2003-12-11) cited in the application	1-6
A	claims 1-9	16-28
Y	EP 1 535 900 A1 (A M S A ANONIMA MATERIE SINT E [IT]) 1 June 2005 (2005-06-01) cited in the application	7-15
A	claims 1,10,11; example 5	16-28
Y	WO 2004/018408 A1 (GLENMARK PHARMACEUTICALS LTD [IN]; NAIK SAMIR JAIVANT [IN]; KULKARNI P) 4 March 2004 (2004-03-04) cited in the application claim 1; examples 1,6	7-15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
3 October 2007	10/10/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	VOYIAZOGLOU, D

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/001301

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 1 496 048 A1 (AJINOMOTO KK [JP]) 12 January 2005 (2005-01-12) claims 1-19; examples 4,5	1-6, 16-28

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